A. Summary of Amendment to the Claims

By the present Amendment, Claims 100, 101, 103, and 113-135 have been amended, Claims 107, 112, 117, and 136 cancelled, and Claims 137-140 added. No new matter within the meaning of 35 U.S.C. §132 (a) has been introduced by the foregoing amendments.

Claim 100 has been amended to specify that the particles comprise microcrystals with a non-hygroscopic inner crystalline core, comprising coprecipitant molecules and an outer coating comprising at least one bioactive molecule. Support for the amendment is found in the published PCT application from which the application claims priority on page 1, lines 5-7.

Claims 100 and 111 have also been amended to specify that the coprecipitant is non-polymeric. This is consistent with the language in Claim 114 (which specifies that the coprecipitant is selected from the group consisting of amino acids, zwitterions, peptides, sugars, buffer components, organic salts, inorganic salts, and derivatives and combinations thereof), as well as the language found in paragraph [0057] of the specification as published.

Claims 101 and 103 were amended to correct a minor enablement issue, namely, the presence of a broad range and a narrow range in the same claim.

Withdrawn Claims 113-135 have been amended to be in the form of method claims, depending, directly or indirectly, from Claim 100. As the claims have been amended to depend from the elected group (method claims rather than composition claims), Applicants respectfully request that the withdrawal of these claims reversed, and that the claims be considered on the merits.

New Claim 137 specifies that the bioactive material is selected from the group consisting of peptides, polypeptides, proteins, nucleic acids, sugars, vaccine components, derivatives thereof, and combinations thereof.

New Claims 138 and 139 were added to include the limitations removed from Claims 101 and 103.

Claim 140 depends from Claim 122, and specifies that the protein is Hib, the vaccine is mumps, measles, or rubella, and the modern flu vaccine components are MV A

vectored influenza vaccine. The spelling of Hib is corrected from the original language in Claim 122, HIB. Those of skill in the vaccine art know that Hib stands for Haemophilus influenzae type b, so this is merely the correction of a minor typographical error.

Claim 124 as amended replaces the duplicate entry of "a crystalline core of valine and a coating of diphtheria toxoid" with "a crystalline core of valine and a coating of tetanus taxoid." Support for this claim is found, at least, in paragraph [0276] of the specification as published, which states:

> PCMCs were made using ovalbumin, Diptheria Toxoid and Tetanus Toxoid with either D,L-valine or L-glutamine as the core crystalline material.

The language in paragraph [0279] differentiates the PCMCs made using either diphtheria toxoid or tetanus toxoid (paragraph [0276]) with those including a mixture of diphtheria toxoid and tetanus toxoid, as evidenced by the title of the section:

> **Mixed** Diptheria Toxoid (DT), Tetanus Toxoid (TT) and Ovalbumin Coated Microcrystals
>
> (emphasis added)

A number of other claims were amended to remove "such as" language, as such would be deemed non-enabling.

Thus, the amendments made herein are fully consistent with and supported by the originally-filed disclosure of this application.

B. Rejections under 35 U.S.C. 112, Second Paragraph

Claims 101 and 103 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite, on the basis that the claims include a broad range together with a narrow range that falls within the broad range. The claims have been amended to remove the narrow ranges, thus obviating this objection.

C. Rejections under 35 U.S.C. 102 (b)

Claims 100-111 were rejected under 35 U.S.C. 102 (b) as anticipated by U.S. Patent No. 5,945,126 to Thanoo et al. ("Thanoo").

The Claimed Subject Matter

Claims 100-111 are directed to a continuous method of forming particles. The method involves:

(a) providing a continuous stream of an aqueous solution comprising non-polymeric coprecipitant molecules and bioactive molecules, each coprecipitant molecule substantially having a molecular weight of less than 4kDa, wherein the aqueous solution is capable of forming a coprecipitate which comprises the coprecipitant and bioactive molecules with a melting point of above about 90°C;

(b) rapidly admixing the continuous stream of bioactive molecule/coprecipitant molecule solution with a greater volume of a continuous stream of a substantially water miscible organic solvent such that the coprecipitant and bioactive molecules coprecipitate from solution forming particles which comprise microcrystals with a non-hydroscopic inner crystalline core comprising coprecipitant molecules and an outer coating comprising at least one bioactive molecule, wherein the continuous streams are mixed in a continuous flow process; and

(c) optionally isolating the particles from the organic solvent.

Applicants note that Claims 113-135 have been amended to also depend from Claim 100. The arguments provided below with respect to Claims 100-112 apply as well to Claims 113-135.

Thanoo

Thanoo discloses a method for continuously mixing a dispersion of a polymer and an active agent with another solvent, such that the dispersed polymer droplets solidify and entrap the active agent within them in the form of microspheres. Thanoo refers to the process as an emulsification process (see the Abstract).

The method is said to be particularly suited to high molecular weight polymers, and is exemplified with polymers of MW 30,000-70,000 (Example 1). Lower molecular weight polymers are said to be "typically associated with slower solidification because the polymer tends to be more soluble" (col. 5, line 55).

Thanoo does not teach, disclose or suggest using dispersants other than polymers. The polymers are required to be soluble in a solvent that is immiscible with water, such as methylene chloride, chloroform, ethyl acetate, substituted pyrrolidone, and the like (Col. 6, line 46). The particles produced are described as "spherical and ranging from porous to non-porous" (Example 1). The active agent is incorporated within the polymer and the polymer is chosen such that it is poorly water soluble and has to biodegrade before the active agent is released.

Analysis

The method disclosed by Thanoo is very different from the method in the claims as amended. The coprecipitants are non-polymeric, and have molecular weights less than 4 KDa, which distinguishes them from the dispersants taught by Thanoo, which are polymers with a preferred weight range of 30,000-70,000.

Further, with respect to Claim 114 as amended, the coprecipitants are amino acids, zwitterions, peptides, sugars, buffer components, organic and inorganic salts, and combinations thereof, none of which are disclosed or suggested by Thanoo.

With respect to Claim 102, the coprecipitants are water-soluble, and insoluble in the water immiscible solvent, and therefore cannot be dispersed in the way described by Thanoo.

The particles are produced by a co-precipitation process, not an emulsion process, and have the bioactive agent coated on their surface, rather than being entrapped within. The particles disclosed dissolve rapidly into aqueous solution, and thus do not need to be biodegraded to release the active agents. Thus, the compositions used, the processes used, and the particles produced are all different. The only element of overlap is that the particles are prepared by a continuous process. However, since the method used and the particles produced by the method are completely different in nature, there is no reason *a priori* to suppose bioactive coated crystals could be prepared by continuous precipitation.

Additional evidence in support of patentability is provided in the form of experimental data. Experiments were performed using lactose or potassium sulfate as the coprecipitant, and using catalase, pepsin, trypsin, or albumin as the protein, to form protein-coated microspheres (referred to as PCMC). The data show that the particles showed a high degree of incorporation of active agent (on the surface rather than within a capsule or dispersed in a polymer matrix), and had a relatively homogenous size distribution.

CONCLUSION

Based on the foregoing, Claims 100-106, 108-111, 113-116, 118-135, and 137-140 are in form and condition for allowance. Prompt acknowledgement of same is earnestly solicited. Rejoinder of some or all of the composition claims is respectfully requested. However, if the method claims are considered allowable, and no rejoinder is possible, the Examiner is encouraged to contact the undersigned to effect cancellation of the withdrawn claims and facilitate allowance.

If any issues require further resolution, the Examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss same.

Respectfully submitted,

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